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First Total Synthesis of 1,3-Diacetyl- and -Dibutyroyl-2-oleoylglycerol, Previously Isolated From Natural Products

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Abstract

The first total synthesis of 1,3-diacetyl-2-oleoylglycerol and 1,3-dibutyroyl-2-oleoylglycerol is described in two steps starting from 1,3-dichloropropan-2-ol. These two glycerides were previously described by hemi-synthesis from natural products.

We describe the total synthesis of two symmetrical triglycerides, 1,3-diacetyl-2-oleoylglycerol (**1a**) and 1,3-dibutyroyl-2-oleoylglycerol (**1b**) (Figure 1), starting from commercialy available 1,3-dichloropropan-2-ol (**2**). Compounds **1a** and **1b** could be potentially interesting in the prevention of cardiovascular diseases.

The 1,3-acetylated triglyceride **1a** was first isolated from a yeast, *Lipomyces starkeyi* Lodder & Kreger-van Rij (Smith et al 1995), grown in a medium containing 1,2-propanediol followed by acetolysis (Suzuki & Hasegawa 1974). In our work, the 1,3-butyroyl triglyceride **1b** and the 1,3-acetylated triglyceride **1a** were prepared in two steps by hemi-synthesis from a microorganism oil rich in docosahexaenoic acid (Bayon & Dolmazon 1996). The oil was a clear yellow–orange liquid (triglyceride) prepared from a marine dinoflagellate, *Crypthecodinium cohnii* (Seligo) Javornicky (Javornicky 1962), which is a non-photosynthetic and non-toxic marine dinoflagellate rich in triacylglycerols (Henderson et al 1988; Henderson & Mackinlay 1991). This heterotrophic marine protoctista (Margulis 1988) is principally localized on rotting *Fucus thalli*, on the littoral of the Baltic Sea, the Atlantic Ocean and the Mediterranean Sea.

Materials and Methods

Chemistry

Melting points were determinated on a Kofler block and are uncorrected. IR spectra were recorded on a Genesis Series FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol JNM-LA 400 spectrometer (400 MHz) using $CDCl_3$ or d_6-DMSO as solvent. Chemical shifts refer to tetramethylsilane which was used as an internal reference. Key: s = singlet, d = doublet, t = triplet, dd = double doublet, qt = quintuplet, sx = sextuplet, m = multiplet. Mass spectra were recorded on a Jeol D 300 instrument using a direct inlet system and electron-impact ionization. Silica gel 60 (70–230 mesh) was used for column chromatography. Elemental analyses (C, H) were performed by INSA (Rouen, France), and agreed with the proposed structures within $\pm 0.3\%$ of the theoretical values.

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*2-Chloro-1-(chloromethyl)ethyl oleate (**3**)*

The reaction between 1,3-dichloropropan-2-ol (**2**) (15 g, 0·116 mol) and oleoyl chloride (30·09 g, 0·10 mol) was completed by heating the mixture at 100°C for 4 h under stirring. The reaction mixture was then cooled and extracted with diethyl ether. The organic layer was washed with water, twice with aqueous sodium bicarbonate, dried over sodium sulphate, charcoaled and evaporated to dryness to give **3** as an orange oil (yield 69%); IR (KBr) ν: 1745 cm^{-1} (CO); ^{1}H NMR ($CDCl_3$) δ: 0·87 (3H, t, J = 6·77, CH_3 oleoyl), 1·28 (22H, m, 11 CH_2 oleoyl), 1·64 (2H, m, CH=CH–CH_2), 1·96 (1H, m, CH_2–CH=CH), 2·00 (1H, m, CH_2–CH=CH), 2·37 (2H, t, J = 7·50, CH_2–CO), 3·74 (2H, d, J = 5·14, CH_2–CH–CH_2), 3·76 (2H, d, J = 5·14, CH_2–CH–CH_2), 5·18 (1H, qt, J = 5·14, CH_2–CH–CH_2), 5·35 (1H, m, CH=CH), 5·38 (1H, m, CH=CH).

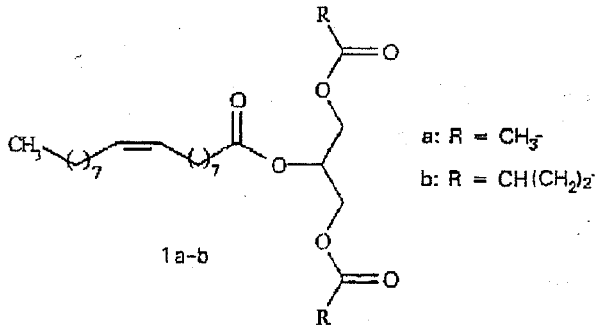

Figure 1 General structure of compounds **1a** and **1b**.

*General procedure for preparation of silver acetate (**4a**) and silver butyrate (**4b**)*
To a solution of acetic acid or butyric acid (0·17 mol) in 500 mL ethanol, were added 28% aqueous ammonia (23·7 mL, 0·17 mol) and silver nitrate (28·92 g, 0·17 mol) dissolved in twice its weight of water. After stirring for 4 h at room temperature, the precipitate thus formed was filtered off, washed with ethanol and dried at 60°C for several hours.

*Silver butyrate (**4b**).* White–grey crystals (yield 51%); mp 254°C; IR (KBr) ν: 1565 cm^{-1} (COOAg); ^{1}H NMR (d$_6$-DMSO) δ: 0·88 (3H, t, J = 7·42, CH_3), 1·54 (2H, sx, J = 7·42, CH_2), 2·13 (2H, t, J = 7·42, CH_2–CO); ^{13}C NMR (d$_6$-DMSO) d: 13·91 (CH$_3$), 19·47 (CH$_2$), 38·65 (CH$_2$), 177·27 (COOAg).

General procedure for preparation of 1,3-diacetyl-2-oleoylglycerol (1a) and 1,3-dibutyroyl-2-oleoylglycerol (1b)
Silver acetate (**4a**) or silver butyrate (**4b**) (0·0152 mol) were mixed with 2-chloro-1-(chloromethyl)ethyl oleate (**3**) (0·00508 mol), with the aid of diethyl ether. The ether was removed by warming on a water-bath, and the mixture heated at 170°C for 8 h with occasional stirring. When cold, the product was extracted with diethyl ether and silver chloride was filtered off. The organic layer was then washed twice with aqueous sodium bicarbonate, then with water, dried over magnesium sulphate, charcoaled and evaporated to dryness. The brown oily residue was twice chromatographed on a silica-gel column, eluting with diethyl ether–hexane (20 : 80, v/v) for the first column and with ethyl acetate–hexane (20 : 80, v/v) for the second.

*1,3-Diacetyl-2-oleoylglycerol (**1a**).* Colourless oil (yield 30%); IR (KBr) ν: 1745 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) δ: 0·81 (3H, t, J = 6·75, CH_3 oleoyl), 1·21 (22H, m, 11 CH_2 oleoyl), 1·53 (2H, m, CH=CH–CH_2), 1·89 (1H, m, CH_2–CH=CH), 1·94 (1H, m, CH_2–CH=CH), 2·01 (6H, s, 2 CH_3CO acetyl), 2·26 (2H, t, J = 7·40, CH_2–CO oleoyl), 4·08 (2H, dd, J = 11·90 and 5·90, CH_2–CH–CH_2), 4·21 (2H, dd, J = 11·90 and 4·15, CH_2–CH–CH_2), 5·19 (1H, m, CH$_2$–CH–CH$_2$), 5·27 (1H, m, CH=CH), 5·30 (1H, m, CH=CH); ^{13}C NMR (CDCl$_3$) δ: 14·04 (CH$_3$ oleoyl), 20·69 (2 CH$_3$–CO acetyl), 22·62 (CH$_2$), 24·77 (CH$_2$), 27·08 (CH$_2$), 27·15 (CH$_2$), 29·03 (CH$_2$), 29·11 (CH$_2$), 29·25 (CH$_2$), 29·29 (CH$_2$), 29·41 (CH$_2$), 29·45 (CH$_2$), 29·59 (CH$_2$), 29·68 (CH$_2$), 32·20 (CH$_2$), 34·02 (CH$_2$–CO oleoyl), 62·10 (2 COO–CH$_2$), 68·84 (COO–CH), 129·78 (CH=CH), 130·40 (CH=CH), 170·40 (2 CO acetyl), 173·02 (CO oleoyl); m/z (EI) 440 (M$^+$), other major fragments; 380, 264, 227, 171, 159, 137, 117, 98. Calculated for $C_{25}H_{44}O_6$: C, 68·08; H, 9·98. Found: C, 68·25; H, 10·11%.

*1,3-Dibutyroyl-2-oleoylglycerol (**1b**).* Pale yellow oil (yield 21%); IR (KBr) ν: 1745 cm^{-1} (CO); ^{1}H NMR (CDCl$_3$) δ: 0·88 (3H, t, J = 6·75, CH_3 oleoyl), 0·95 (6H, t, J = 7·45, 2 CH_3 butyroyl), 1·29 (22H, m, 11 CH_2 oleoyl), 1·63 (2H, m, CH=CH–CH_2), 1·67 (4H, sx, J = 7·45, CH_2 butyroyl), 1·97 (1H, m, CH_2–CH=CH), 2·01 (1H, m, CH_2–CH=CH), 2·30 (4H, t, J = 7·45, 2 CH_2–CO butyroyl), 2·31 (2H, t, J = 7·30, CH_2–CO oleoyl), 4·15 (2H, dd, J = 11·88 and 5·93, CH_2–CH–CH_2), 4·30 (2H, dd, J = 11·88 and 4·33, CH_2–CH–CH_2), 5·27 (1H, m, CH$_2$–CH–CH$_2$), 5·34 (1H, m, CH=CH), 5·38 (1H, m, CH=CH); ^{13}C NMR (CDCl$_3$) δ: 13·58 (2 CH$_3$ butyroyl), 14·08 (CH$_3$ oleoyl), 18·31 (2 CH$_2$ butyroyl), 22·66 (CH$_2$), 24·85 (CH$_2$), 27·14 (CH$_2$), 27·19 (CH$_2$), 29·04 (CH$_2$), 29·16 (CH$_2$), 29·24 (CH$_2$), 29·26 (CH$_2$), 29·49 (CH$_2$), 29·62 (CH$_2$), 29·73 (CH$_2$), 31·87 (CH$_2$), 32·57 (CH$_2$), 34·16 (CH$_2$–CO oleoyl), 35·88 (2 CH$_2$–CO butyroyl), 62·05 (2 COO–CH$_2$), 68·83 (COO–CH), 129·66 (CH=CH), 130·00 (CH=CH), 172·84 (CO oleoyl), 173·07 (2 CO butyroyl); m/z (EI) 496 (M$^+$), other major fragments; 408, 395, 337, 264, 215, 145, 98, 71. Calculated for $C_{29}H_{52}O_6$: C, 70·12; H, 10·55. Found: C, 70·29; H, 10·78%.

Results and Discussion

Chemistry

The reaction sequence used to prepare 1,3-diacylated and -butyroylated triglycerides (**1a** and **1b**)

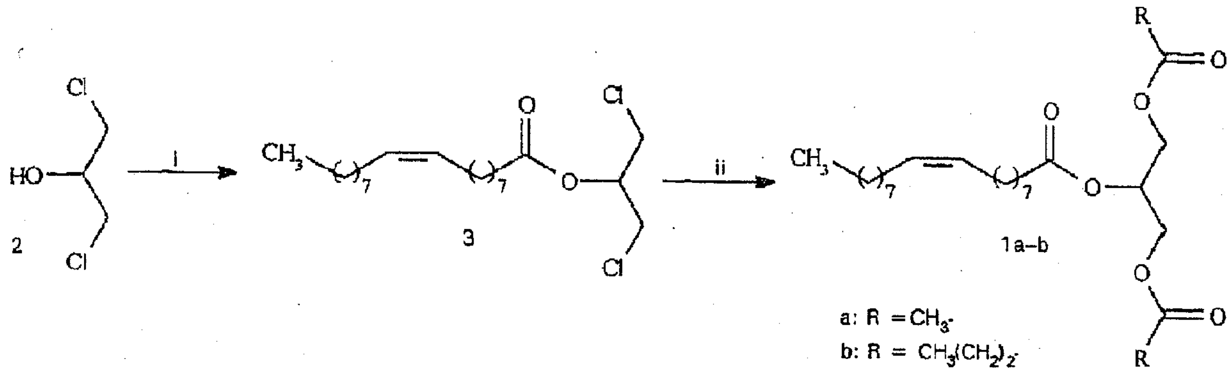

Figure 2. Synthesis of 1,3-diacetyl-2-oleoylglycerol (**1a**) and 1,3-dibutyroyl-2-oleoylglycerol (**1b**). Reagents: i. (*Z*)-$CH_3-(CH_2)_7-CH=CH-(CH_2)_7-COCl$; ii. $CH_3-COOAg$ or $CH_3-(CH_2)_2-COOAg$.

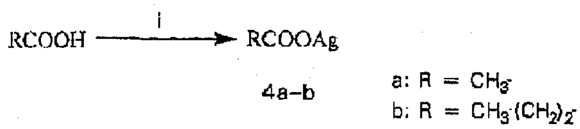

Figure 3. Synthesis of silver acetate (**4a**) and silver butyrate (**4b**). Reagent: i. $AgNO_3$, NH_4OH, C_2H_5OH.

began from commercialy available 1,3-dichloropropan-2-ol (**2**) and was achieved in two steps with 21 and 15% overall yield, respectively. 2-Chloro-1-(chloromethyl)ethyl oleate (**3**) (Humnicki 1929; Bougault 1932; Schuster 1933) was obtained in 69% yield by heating oleoyl chloride at 100°C with 1,3-dichloropropan-2-ol (**2**) according to Grün's method (Grün 1910). The derivative (**3**) was subjected to nucleophilic substitution with 3 molar equivalent, silver acetate (**4a**) or silver butyrate (**4b**). This led to symmetrical 1,3-diacetyl-2-oleoylglycerol (**1a**) and 1,3-dibutyroyl-2-oleoylglycerol (**1b**) (Whitby 1926; Bhati et al 1983), respectively. The silver salts of acetic or butyric acids (**4a** or **4b**) reacted very readily with the alkyl dihalide (**3**) yielding triesters **1a** and **1b** (Figure 2).

Silver acetate (**4a**) and silver butyrate (**4b**) (Peterson et al 1952) were prepared by reaction of silver nitrate with acetic acid or butyric acid in the presence of aqueous ammonia in ethanol (Whitby 1926; Figure 3).

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